hydrOCHLOROTHIAZIDe

Newborn use only

2021

Alert	Not to be confused with chlorothiazide.
Indication	Chronic lung disease. Heart failure. Fluid overload. Hypertension. In conjunction with diazoxide to counter fluid retention.
Action	Inhibition of sodium reabsorption in distal nephron, leading to loss of water, sodium, potassium, magnesium, chloride, phosphate and bicarbonate.
Drug type	Thiazide diuretic.
Trade name	Dithiazide
Presentation	Oral suspension manufactured by Pharmacy 1 mg/mL, 2 mg/mL, 5 mg/mL or 10 mg/mL; 25 mg tablets
Dose	1 to 2 mg/kg/dose every 12-24 hours (consensus opinion); **Consider alternate day dosing:** 2 mg/kg/dose every 48 hours (consensus opinion).
Dose adjustment	Therapeutic hypothermia – Not applicable. ECMO – No information. Renal impairment – half life is prolonged with renal impairment (adult data) Hepatic impairment – Not applicable.
Maximum dose	4 mg/kg/day
Total cumulative dose	
Route	Oral
Preparation	Oral suspension
Administration	Administer undiluted with feeds to improve absorption.
Monitoring	Urine output and weight. Serum sodium, potassium, calcium, phosphorous and glucose.
Contraindications	Hypersensitivity to any component. Thiazide diuretic contains a sulphonamide moiety. While it has long been considered that allergic cross-reactivity may exist between sulfonamide antibiotics and other sulfonamide drugs, this is actually unlikely because of the structural differences.[11]
Precautions	Hypokalaemia. Hyponatraemia. Displaces bilirubin so caution required in jaundiced infants.
Drug interactions	Hypokalaemia may increase toxic effects of digitalis. Concurrent use of SOTALOL and DIURETICS may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest). Concurrent use of FLECAINIDE and HYDROCHLOROTHIAZIDE may result in increased risk of electrolyte imbalance and subsequent cardiotoxicity.
Adverse reactions	Hypokalaemia; hyponatraemia; hyperglycaemia; hyperuricaemia; hypercalcaemia. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.
Compatibility	N/A
Incompatibility	N/A
Stability	N/A
Storage	Check with local pharmacy.
Excipients	
Special comments	Improves respiratory function in preterm infants with or developing chronic lung disease. Used in conjunction with diazoxide to counter diazoxide-induced sodium and fluid retention. Increases urine output, potassium and phosphorus excretion. Urinary calcium excretion may be decreased.1 Usually used in combination with spironolactone to reduce potassium loss. Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. The mean plasma half-life is prolonged with renal impairment.[3]
Evidence	**Efficacy:** <u>In preterm infants > 3 weeks of age with chronic lung disease:</u> Acute and chronic administration of distal diuretics improve pulmonary mechanics.[4] A single study showed thiazide and spironolactone

	decreased the risk of death in infants who did not have access to corticosteroids, bronchodilators or aminophylline.[5] (LOE I, GOR C) Trials used hydrochlorothiazide doses ranging from 3 to 4 mg/kg/day divided 12 hourly in combination with spironolactone. Concomitant therapy with diazoxide: Diazoxide can cause sodium and fluid retention and concomitant use of thiazide diuretics is recommended to counter this effect.[6-9] The fluid retention from diazoxide is mostly observed in the neonatal period and may cause cardiac failure; hence the concurrent use of a thiazide diuretic in neonates. However, routine use of a thiazide diuretic is not necessary in older children when there is no evidence of fluid retention.[7] **Pharmacokinetics and pharmacodynamics:** Oral bioavailability in adults is approximately 60–70% and the peak concentrations in plasma occur within 1.5 to 4 hours following an oral dose.[3] (LOE IV) The mean plasma half-life of hydrochlorothiazide in adults has been reported to be from 3.2 to 13.1 hours [2](LOE IV GOR C) and is prolonged with renal impairment. [3] (LOE IV GOR C) The pharmacokinetics have not been reported in infants. **Safety:** Preterm infants receiving hydrochlorothiazide in combination with spironolactone may have an increased need for sodium and potassium supplementation.[5] (LOE II GOR B) Whether alternative day dosing of hydrochlorothiazide is associated with reduced need for sodium and potassium supplementation, as with alternate day furosemide dosing,[10] has not been tested in clinical trials. Unlike furosemide, hydrochlorothiazide has not been associated with hearing loss or nephrocalcinosis in newborn infants.[4] (LOE II GOR B)
Practice points	
References	1. Kao LC, Warburton D, Cheng MH, Cedeno C, Platzker AC, Keens TG. Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: results of a double-blind crossover sequential trial. Pediatrics. 1984;74:37-44. 2. Chen TM, Chiou WL. Large differences in the biological half-life and volume of distribution of hydrochlorothiazide in normal subjects from eleven studies. Correlation with their last blood sampling times. Int J Clin Pharmacol Ther Toxicol. 1992;30:34-7. 3. Van Wart SA, Shoaf SE, Mallikaarjun S, Mager DE. Population-based meta-analysis of hydrochlorothiazide pharmacokinetics. Biopharm Drug Dispos. 2013;34:527-39. 4. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev. 2011:CD001817. 5. Albersheim SG, Solimano AJ, Sharma AK, Smyth JA, Rotschild A, Wood BJ, Sheps SB. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. J Pediatr. 1989;115:615-20. 6. Banerjee I, Avatapalle B, Padidela R, Stevens A, Cosgrove KE, Clayton PE, Dunne MJ. Integrating genetic and imaging investigations into the clinical management of congenital hyperinsulinism. Clinical endocrinology. 2013;78:803-13. 7. Senniappan S, Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. Journal of inherited metabolic disease. 2012;35:589-601. 8. Hu S, Xu Z, Yan J, Liu M, Sun B, Li W, Sang Y. The treatment effect of diazoxide on 44 patients with congenital hyperinsulinism. Journal of Pediatric Endocrinology and Metabolism 2012;25:1119–1122. 9. Yoshida K, Kawai M, Marumo C, Kanazawa H, Matsukura T, Kusuda S, Yorifuji T, Heike T. High prevalence of severe circulatory complications with diazoxide in premature infants. Neonatology 2014;105(3): 166-171. 10. Rush MG, Engelhardt B, Parker RA, Hazinski TA. Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. J Pediatr. 1990;117:112-8. 11. Smith WB. Sulfur allergy label misleading. Australian Prescriber 2008;31:8-10.

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